Title

The Berkeley Contact Lens Extended Wear Study. Part II : Clinical results.

Journal

Ophthalmology, 108(8)

ISSN

0161-6420

Authors

Polse, KA
Graham, AD
Fusaro, RE
et al.

Publication Date

2001-08-01

DOI

10.1016/s0161-6420(01)00628-5

Peer reviewed

The Berkeley Contact Lens Extended Wear Study: Part II

Clinical Results

Kenneth A. Polse, OD, MS,[1] Andrew D. Graham, MS,[1] Robert E. Fusaro, PhD, JD,[2] Cheslyn M. Gan, OD,[1] Reuben K. Rivera, OD, MS,[1] Meng C. Lin, OD,[1] Timothy L. Sanders, OD,[1] Nancy A. McNamara, OD, PhD,[1] Judy S. Chan, OD, MS[1]

Objective: To describe the principal clinical outcomes associated with 12 months use of rigid gas-permeable (RGP) extended wear contact lenses and address two primary study questions: (1) does extended wear (EW) of high oxygen transmissibility (Dk/t) RGP lenses reduce the incidence of ocular complications, and (2) does the wearing of high-Dk/t lenses reduce the rate of failure to maintain 6-night RGPEW over 12 months?

Design: A randomized, concurrently controlled clinical trial.

Intervention: Subjects who adapted to EW with high Dk (oxygen permeability) RGP lenses were randomized to either high Dk or medium-Dk RGP lenses for 12 months of 6-night EW.

Main Outcome Measures: Contact lens-associated keratopathies (CLAK), changes in refractive error and corneal curvature, and survival in EW.

Results: Two hundred one subjects were randomized to medium or high-Dk lenses for 12 months of EW. Sixty-two percent of the subjects in each group completed 12 months of EW; however, the probability of failure was significantly greater for the medium-Dk group. Although the risk of complications was similar for the two groups, the number of CLAK events that led to termination were 16 versus 5 for the medium-Dk and high-Dk groups, respectively. This suggests that the type of adverse response or the inability to reverse an adverse event was different for the group being exposed to the lower oxygen dose.

Conclusions: The level of oxygen available to the cornea has a significant impact on maintaining successful RGP extended contact lens wear, but not on the initial onset of CLAK. The number of clinical events leading to termination was substantially higher for the medium Dk group, which suggests that corneal hypoxia is an important factor in the development of CLAK. Although overnight contact lens wear should be recommended with caution and carefully monitored for early detection of ocular complications, it appears that high-Dk RGP lenses can be a safe and effective treatment for correction of refractive error for most individuals who can adapt to EW. *Ophthalmology 2001;108:1389–1399 © 2001 by the American Academy of Ophthalmology.*

The Berkeley Contact Lens Extended Wear Study (CLEWS) was a randomized, concurrently controlled clinical trial designed to examine the effects of corneal hypoxia on ocular complications arising from the extended wear of rigid gas-permeable (RGP) contact lenses of either medium or high oxygen permeability (Dk). In part I of this report, we described the background, design, and implementation of CLEWS. In that article, we showed that the distributions of lens oxygen transmissibility (Dk/t) in the lenses assigned to the two study groups were completely disjoint (Fusaro RE, Polse KA, Graham AD, The Berkeley Contact Lens Extended Wear Study. Part I: Study Design and Conduct), confirming that subjects randomized to the medium-Dk lens group were subject to a greater degree of hypoxia. Providing different oxygen levels to each group permitted us to explore the association between hypoxic dose and certain clinical outcomes associated with 12 months of rigid gas-permeable extended wear (RGPEW) by addressing two primary study questions:

1. Does extended wear of high-Dk RGP lenses, rather than medium-Dk RGP lenses, reduce the incidence of ocular complications?
2. Does the wearing of high-Dk RGP lenses, rather than medium-Dk RGP lenses, reduce the rate of failure to maintain 6-night RGPEW?

Originally received: August 25, 2000.
Accepted: March 6, 2001. Manuscript no. 200499.

[1] Morton D. Sarver Laboratory for Cornea and Contact Lens Research, School of Optometry, University of California, Berkeley, California.

[2] Division of Public Health Biology and Epidemiology, School of Public Health, University of California, Berkeley, California.

Supported by the National Eye Institute, National Institutes of Health, Bethesda, Maryland (grant no.: EY07728); Concise Contact Lens Co., San Leandro, California; and Paragon Vision Sciences, Mesa, Arizona.

The authors have no proprietary interests in this article.

Reprint requests to Kenneth A. Polse, OD, MS, School of Optometry, University of California, Berkeley, CA 94720-2020.

ISSN 0161-6420/01/$–see front matter
PII S0161-6420(01)00628-5

Materials and Methods

In this section, we briefly review the CLEWS design, explain our strategy for quantifying various types of ocular complications for analysis, and present the statistical methodology we used in analyzing the CLEWS clinical trial data. The reader is encouraged to refer to part I for a more comprehensive treatment of the issues relevant to assessing the integrity of the data and to interpreting and generalizing the results presented in this companion article.

Overview of the Berkeley Contact Lens Extended Wear Study Design

The Berkeley CLEWS was a randomized, concurrently controlled clinical trial designed to evaluate the hypothesis that ocular morbidity in RGPEW is associated with the level of corneal hypoxia induced by the lenses. The trial was structured with three main stages. In stage 1, prospective subjects were oriented to the goals and procedures of the study and then examined to determine eligibility. In stage 2, subjects were adapted to contact lens wear, beginning with daily wear and progressing to full-time (i.e., 6 nights per week) extended wear (EW). Those who were able to achieve full-time EW then proceeded to stage 3 and were randomly assigned either medium- or high-Dk lenses for 12 months of full-time EW. Stage 3 subjects attended quarterly visits, during which optometrists conducted detailed interviews, slit-lamp examinations, visual acuity assessments, and refractive error (RE) and corneal curvature (K) readings. Results of stage 1 and stage 2 recruitment and retention efforts and baseline subject data are presented in part I. The clinical outcomes for the two randomized subject groups are compared in this article.

Contact Lens-associated Keratopathy

To compare the incidence of ocular complications between the two lens groups, it was necessary to define contact lens-associated keratopathy (CLAK). We asked six experienced contact lens practitioners who were not associated with CLEWS and who were unaware of any CLEWS interim results to complete a survey detailing the severity of complications that they believed would typically require intervention (e.g., changing lens parameters, prescribing medications, temporarily discontinuing lens wear to allow the complication to subside, completely terminating lens wear). The survey respondents were presented with 17 possible keratopathies and asked to indicate for each condition the minimum grade of severity (0 = none, 1 = mild, 2 = moderate, 3 = severe) that they would consider an adverse event requiring clinician intervention. Each clinician was also asked to indicate the number of events of lesser severity that, if observed concurrently, would require intervention. Finally, they were asked to indicate the diopters of refractive error (RE) and corneal curvature (K) change from prefitting measurements that they would characterize as an adverse response requiring intervention. The survey results led to the CLAK definitions reported in Table 1.

Our goal was to quantify CLAK in a manner that would reflect the consensus opinion of the outside clinicians and be meaningful in practice (i.e., as adverse responses severe enough to require clinician intervention). Using the survey results, we constructed four increasingly inclusive definitions of CLAK and repeated our analyses using each of these four definitions. With this approach, we were able to assess the ocular response to hypoxic dose while allowing for more or less restrictive definitions of CLAK, thereby facilitating comparison with other studies that may use different criteria in reporting incidences of lens-related complications. Using our first definition of CLAK (type 1), we examined the effects of hypoxic dose on the occurrence of any keratopathy detected by slit-lamp examination in either eye, whose severity equaled or exceeded the average of the six survey responses rounded to the nearest severity grade. Type 1 CLAK also included lens adherence that required changes to the lens parameters. Lens binding that was less frequent or was alleviated by the use of solutions, cleaning or polishing the lens, or further training of the subject in lens care and handling procedures was not considered a type 1 CLAK. Lens adherence was not included in the original survey because it was thought that individuals subject to persistent lens adherence would not be able to complete the EW adaptation period, and therefore adherence would not occur in our randomized subjects. However, a data quality review revealed that several randomized subjects did experience persistent lens binding, thus prompting a manual search of the entire bank of patient records to ascertain all such cases of adherence. Randomization assignment was not revealed during the search, and at the time the decision was made to include lens adherence as a type 1 CLAK, it was not known whether the two Dk groups differed in adherence rate.

We then expanded our definition of CLAK (type 2) to include type 1 CLAK and changes in K or RE from baseline in either eye

Table 1. Definitions of Contact Lens-associated Keratopathy

Keratopathy or Adverse Event	Minimum Value Defined as Contact Lens-associated Keratopathy
Bulbar conjuctiva	
Injection	2
Staining	
Superior	1
Inferior	2
Nasal	2
Temporal	2
Palpebral conjunctival injection	
Superior tarsus	2
Inferior tarsus	2
Hypertrophy	
Superior tarsus	2
Inferior tarsus	2
Corneal staining	
Central	1
Peripheral	2
Corneal infiltrates	
Central	1
Peripheral	1
Microcysts	2
Striae	2
Polymegethism	2
Tear debris	2
Lens adherence	3 times weekly, persistent
Change in corneal curvature	
Horizontal meridian	0.88
Vertical meridian	0.83
Change in refractive error	
Sphere	0.88
Cylinder	0.92
Simultaneous subclinical slit-lamp findings (n)	3
Discomfort and related symptoms	2

Type 1 contact lens-associated keratopathy includes slit-lamp findings and lens adherence; type 2 includes both type 1 responses and changes in corneal curvature or refractive error; type 3 includes both type 2 and multiple, simultaneous subclinical findings; type 4 includes both type 3 and subjective symptoms related to discomfort. Severity grading: 0 = none, 1 = mild, 2 = moderate, 3 = severe.

that exceeded the mean diopters of change indicated by the survey respondents. Our third definition of CLAK (type 3) included three or more simultaneous "subclinical keratopathies" (i.e., observed at the slit lamp, but less severe than the grades qualifying as type 1) in either eye, in addition to type 2 CLAK. Finally, we repeated our analyses using a fourth definition (type 4) that included type 3 CLAK or moderate to severe discomfort, burning, itching, or pain at a regularly scheduled clinical assessment, or these symptoms to such a degree that an unscheduled visit was needed.

Statistical Methods

An attractively simple way to summarize the failure experience of subjects at risk for an adverse event is by the simple proportion of subjects who fail over the course of the study. This approach is inappropriate, however, for several reasons. First, it is inefficient in that it fails to use data concerning the specific times at which failures occurred and, rather, treats all failures within the study period as the same. Second, this approach ignores the fact that only incomplete, or censored, information may be available for some subjects. Subjects may provide partial, right-censored data because they elected to discontinue study participation or were terminated from the study by the clinician for reasons unrelated to study lens wear, such as time commitment, general disinterest, or noncompliance with the study protocol. An unknown number of these subjects may have suffered lens-related adverse events had they been available for the entire 12-month observation period. Subjects were failed for noncompliance by the clinician if they were unable or unwilling to attend the required laboratory visits consistently, if there were frequent lens care or handling problems as a result of failure to follow instructions or if subjects were inconsistent in maintaining their 6-night EW schedule. For subjects who missed scheduled visits and did not contact the laboratory, the Study Coordinator followed a standard procedure for attempting to contact the subject before completing a termination form. Adverse events were defined as initial onset of a CLAK condition (for study question 1) and termination from the study as a result of a type 4 CLAK condition (for study question 2).

To account for censoring, we used the product-limit (Kaplan-Meier) approach[1] to estimate the Dk group-specific survival curves, which characterize the probabilities of successful EW or freedom from complications over time. The homogeneity of the survival curves between Dk groups was assessed using a log-rank test.[1] Estimates of the relative risk of complications or RGPEW failure associated with hypoxic dose were obtained by fitting Cox proportional hazards models.[1] We used the SAS (SAS Institute, Inc., Cary, NC) procedures LIFETEST and PHREG to implement these survival analytic techniques.[2]

It has been suggested that overnight lens wear, particularly with lower-Dk materials, may alter corneal topography.[3,4] We therefore attempted to ascertain whether K or RE in our RGPEW subjects differed between Dk groups or changed over time in either group. We used the SAS procedure MIXED to implement a mixed effects analysis of variance approach to comparing changes from baseline in K (horizontal and vertical meridians) and RE (sphere and cylinder components) in the two Dk groups.[2] We modeled the change from baseline in each of these outcomes with fixed effects for Dk group and visit (3, 6, 9, and 12 months) within each group and a compound symmetric covariance structure to account for the correlations among repeated measurements on the two eyes of each subject across visits. This structure assumes a common covariance among all measurements on a single subject.

Results

Overview

This section is divided into four parts. In the first part, we describe subject participation rates by visit along with the reasons subjects dropped out or were terminated from the study. The second section presents our basic clinical observations, including group trends in RE and K, the specific types of keratopathy encountered, and detailed descriptions of those subjects in each group who had to discontinue overnight lens wear completely because of CLAK. The third section addresses the first of our primary CLEWS questions by comparing the probabilities of the two types of lens wearers remaining free from complications through time and by estimating the relative risk of complications associated with hypoxic dose. Finally, in the fourth section, we address the second of our two primary CLEWS questions by comparing the estimated survival probability curves between groups and estimating the relative risk of failure to maintain EW associated with hypoxic dose.

Subject Retention, Termination, and Loss to Follow-up

Of 2218 subjects who attended an orientation meeting, 545 subjects were deemed eligible and were willing to participate in CLEWS. These subjects were fit with high-Dk lenses for daily wear adaptation. Of the 344 subjects who proceeded from daily wear to EW adaptation, 201 subjects adapted to EW and were randomized to either medium-Dk (n = 103) or high-Dk (n = 98) RGP lenses for 12 months of full-time EW. Our stratified block randomization scheme, detailed in part I of this report, ensured that approximately the same number of subjects were assigned to each lens group at any given point during the study and that ages and genders were balanced between the two groups.

Table 2 shows the number of subjects examined at each quarterly visit in the two groups and the number failing to attend each scheduled assessment. Of the 103 medium-Dk wearers, 24 subjects did not complete the first quarterly visit, and data were collected on the remaining 79 subjects. Of these 24 subjects who did not participate in the 3-month examination, 3 returned for subsequent visits, whereas 21 were either lost to follow-up or failed as a result of complications before the first quarterly visit. The high-Dk group showed a similar pattern; 19 of the 98 randomized subjects failed to complete the first visit, leaving 79 available for 3-month observations. After these relatively large losses of subjects early in the course of follow-up, the number of subjects failing to complete subsequent visits declined. At final count, 64 subjects (62.1%) in the medium-Dk group and 61 subjects (62.2%) in the high-Dk group were able to complete the entire 12 months of RGPEW successfully.

During the postrandomization phase, some subjects required one or more appointments in addition to the quarterly assessments. These unscheduled visits were either initiated by the patient because of a lens-related problem or an ocular symptom or by the clinician at the time of a regularly scheduled clinical assessment as a result of a slit-lamp finding requiring monitoring or follow-up care. The reasons reported for unscheduled visits are shown in Table 3. Over the postrandomization period, there were a total of 91 unscheduled visits from 53 subjects in the medium-Dk group and 77 visits from 42 subjects in the high-Dk group. Replacement of lost lenses was the most common reason for unscheduled visits, although there were a substantial number of visits as a result of onset of adverse symptoms, primarily red eye and foreign body sensation in both groups, discomfort and blurred vision in the medium-Dk group, and pain in the high-Dk group. The most

Table 2. Contact Lens-associated Keratopathy CLEWS Subject Participation

	Medium Oxygen Permeability Group (n = 103)				High Oxygen Permeability Group (n = 98)			
Follow-up Visit (mos)	*3*	*6*	*9*	*12*	*3*	*6*	*9*	*12*
Completed visit	79	73	66	64	79	67	64	61
Did not complete visit	21	7	7	2	18	11	4	2
Cumulative	21	28	35	37	18	29	33	35
Missed visit but returned	3	2	2	2	1	2	1	2

Shown are the numbers of contact lens-associated keratopathy subjects in each randomized study group who completed or failed to complete each scheduled follow-up visit. Occasionally, subjects would miss a scheduled visit without discontinuing study participation (e.g., for an extended vacation) and return to the study for subsequent visits.

common slit-lamp findings at the unscheduled visits were corneal and bulbar conjunctival staining, with few or no occurrences of corneal striae, hypertrophy, infiltrates, microcysts, injection, or polymegethism.

The reasons for termination or drop-out before 12 months in the two study groups are provided in Figure 1. Most failures and drop-outs in both groups occurred within 3 months after randomization, although the reasons for failure differ between the groups. In the high-Dk group, most subjects unavailable for the first quarterly visit (n = 18) either elected to drop out for reasons unrelated to contact lens wear or were terminated for noncompliance, whereas only two subjects failed for lens-related adverse responses. In contrast, in the medium-Dk group, the reasons for failures before the first quarterly visit were nearly evenly divided between those unrelated to lens wear (n = 11) and lens-related adverse responses (n = 10). Over the remaining visits, the medium-Dk group continued to demonstrate comparable numbers of failures for lens-related complications (n = 7) and reasons unrelated to contact lens wear (n = 8). The high-Dk group also continued its pattern of reasons for failure, with far more unrelated to lens wear (n = 14) than lens-related adverse responses (n = 2).

Table 3. Reasons for Unscheduled Visits for Initial Onset of Symptoms (Follow-up Examinations for Previously Identified Conditions Not Included in This Summary)

	Medium Oxygen Permeability Group	High Oxygen Permeability Group
No. subjects requiring unscheduled visits	53	42
Total number of unscheduled visits by these subjects	91	77
No. subjects reporting reason for visit (may be >1 reason, >1 visit per subject, or both)		
Lost lens	20	17
Red eye	16	12
Pain	10	16
Discomfort	16	9
Foreign body sensation	14	11
Blurred vision	12	8
Tearing	10	6
Drying	10	2
Burning	4	8
Itching	5	5
Photophobia	6	4
Cracked/broken lens	2	5
Discharge	4	3
Lens handling problem	1	1

Clinical Observations

In this section, we present further observational data that do not, by themselves, directly address the two primary CLEWS research questions, but nevertheless are of clinical interest. We first report on changes observed in K and RE, then describe the specific types of keratopathy encountered in the two lens groups and present the detailed diagnoses of the 21 subjects failing for lens-related ocular complications. In the two sections that follow this clinically oriented presentation, we apply the appropriate survival analytic techniques to these data to address directly the two primary questions for which CLEWS was designed.

Changes in Refractive Error and Corneal Curvature. To determine whether overnight wear of medium- or high-Dk RGP lenses is associated with changes in K or RE over time, manifest refraction and keratometry readings were performed at the baseline subject evaluation and at each of the quarterly clinical assessments. For both Dk groups, average changes in the spherical refractive component from baseline measurements were small and in the direction of reduced myopia (ranging from 0.12–0.20 diopters [D] at the different visits), and for the cylinder there were small reductions in the astigmatic component (ranging from 0.11–0.15 D). Keratometry for both Dk groups showed modest decreases in power in both the vertical and horizontal meridians (ranging from 0.46–0.51 D). There were no significant Dk group or visit effects on any of these measures within the two Dk groups. In Figure 2, the change from baseline in refractive sphere, using the average of each subject's two eyes, is shown stratified by visit for the medium- and high-Dk groups, illustrating the lack of clinically important changes in corneal topography found in both RE and keratometry measurements. From these results, we concluded that overnight wear of RGP lenses does not significantly affect corneal topography, nor does the oxygen permeability of the lens.

Observations of Lens-related Complications. Table 4 shows the overall number of cases of CLAK observed during the CLEWS clinical trial for each of our definitions, under all four of which a slightly larger number of subjects had complications in the medium-Dk group than in the high-Dk group. Of potential clinical interest are the specific types of slit-lamp findings from up to 1 year of observation of more than 200 RGPEW patients, which are presented in Table 5. By far the most commonly observed keratopathy in both groups was corneal staining, which occurred more often in the central cornea than in the periphery, followed by redness and staining of the conjunctiva (20 cases in the medium-Dk group versus 10 cases in the high-Dk group over all visits). There were 3 cases of corneal infiltrates and 13 cases of moderate-to-severe striae in the medium-Dk group, compared with the high-Dk group in which no infiltrative events and 2 cases of CLAK-grade striae occurred. Lens adherence that required changing lens parameters occurred in subjects in each group. There were

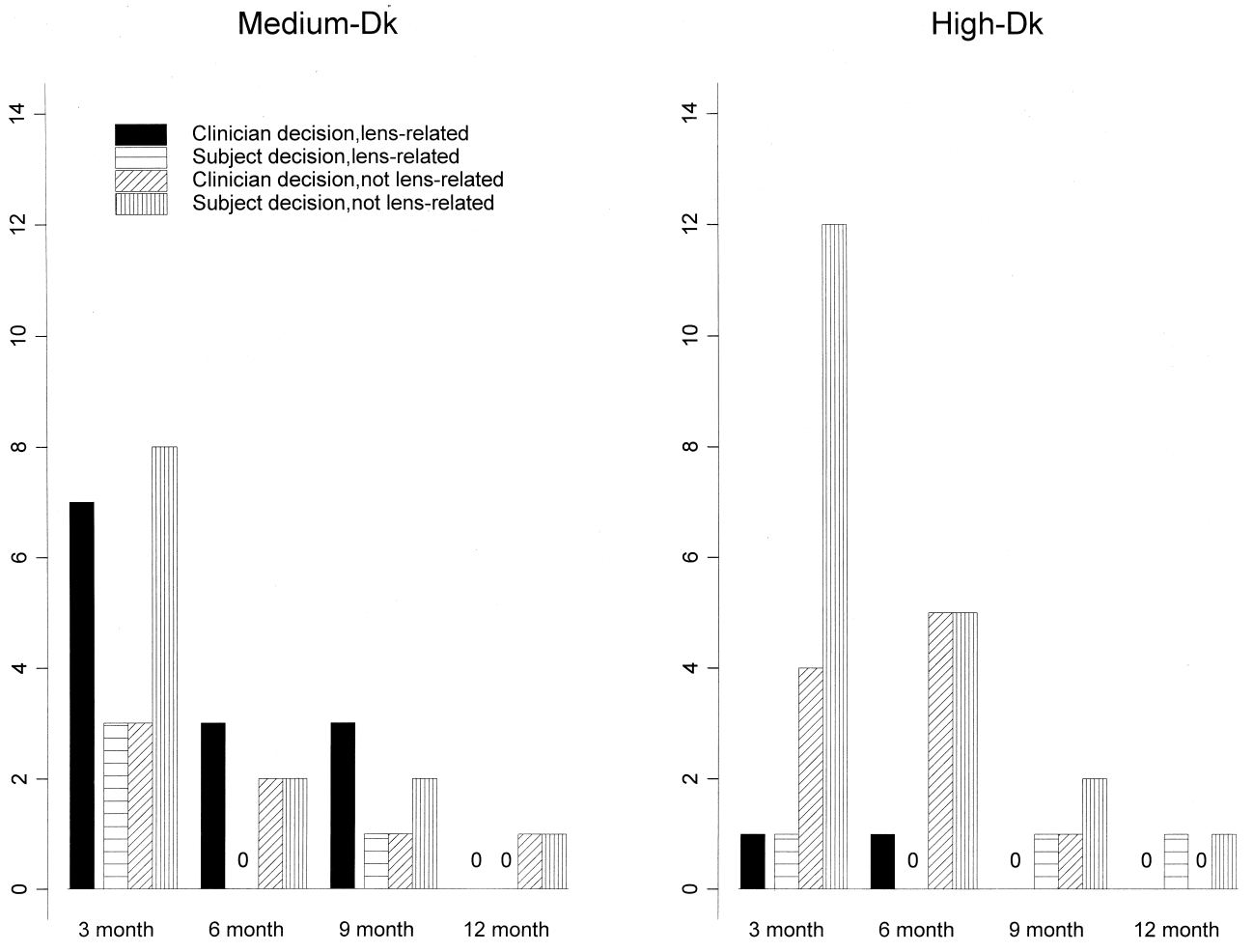

Figure 1. After randomization to the medium or high oxygen permeability (DK) study group, subjects could be dropped from the study by the clinician as a result of lens-related complications that could not be resolved, or for reasons unrelated to wearing the study lenses such as noncompliance with the study protocol. Subjects themselves could elect to discontinue participation for lens-related discomfort if the clinician was unable to resolve the symptom, or for various other reasons unrelated to lens wear (e.g., moving out of the area).

few or no cases of microcysts or polymegethism in either group. It is also interesting that in this study of RGPEW, we did not observe any cases of microbial keratitis, neovascularization, or acute red eye, which often occur in soft contact lens extended wear (SCLEW).[5–7]

Figure 3 shows the days from randomization to complete discontinuation of EW for the 21 subjects who were terminated from the study because of type 4 CLAK, along with the specific causes of failure. In total, 16 subjects in the medium-Dk group were terminated before 12 months of follow-up because of keratopathy or discomfort, whereas only high-Dk subjects failed for reasons directly related to lens wear. Of the 16 medium-Dk group terminations, 5 subjects failed for persistent lens adherence (i.e., after having successfully adapted to EW in stage 2 while wearing the high-Dk adaptation lenses), whereas 1 of the 5 failures in the high-Dk group was the result of adherence. All five cases of persistent lens adherence in the medium-Dk group eventually required complete discontinuation of EW, whereas four of the five adherence cases in the high-Dk group were resolved successfully. Although these clinical observations are suggestive of a greater risk of some lens-related complications, EW failure, or both in the medium-Dk group, censoring resulting from non-CL related factors makes survival analytic methods necessary for unbiased comparisons of the two Dk groups.

Association of Hypoxic Dose with Ocular Complications

In this section, we present the survival analyses for time to initial onset of CLAK for each of the four definitions of CLAK. The number of elapsed days was calculated from the date of dispensing of the randomized study lenses to the date the clinician first observed a CLAK event, which could have occurred at a regularly scheduled clinical assessment or an unscheduled visit; subjects who never exhibited such complications are right-censored at their last observation time 12 months or fewer from randomization. We analyzed the initial onset of CLAK for each subject rather than multiple CLAK events because of the difficulty in distinguishing unique events from recurrence of previously treated conditions and because attempts to ameliorate the first observed keratopathy often included disruption of the EW schedule for varying periods of time. Furthermore, termination from the study because of a CLAK event censors such subjects with respect to possible subsequent events, but is not independent of the risk of such subsequent CLAK events as is required for the use of standard survival analytic techniques.

Figure 4 depicts the survival curves characterizing the probability of remaining free from complications under the two different levels of hypoxia induced by the study lenses. The height of a

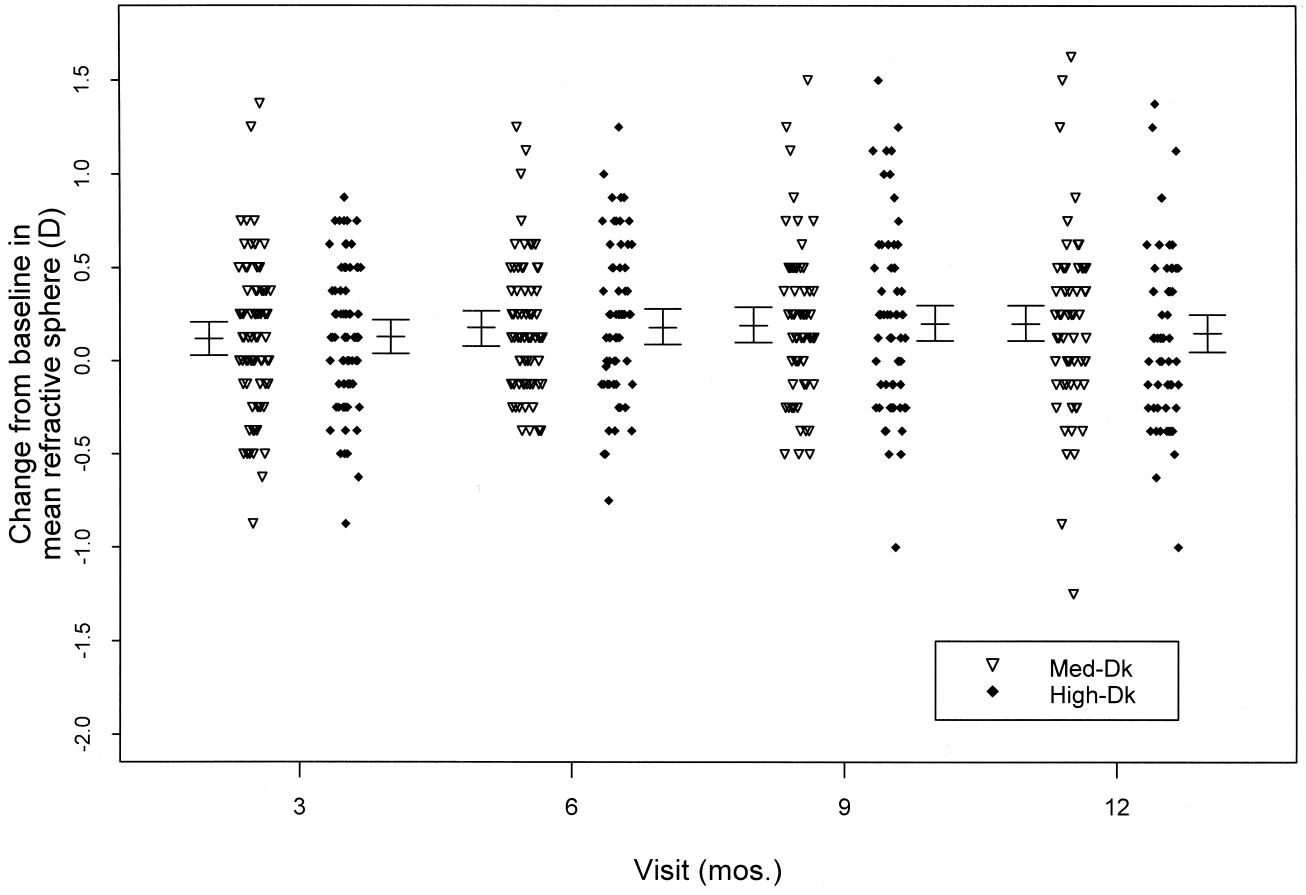

Figure 2. Shown is the change from baseline in refractive sphere in the medium and high oxygen permeability (DK) groups at each visit. The bars represent the least squares means and 95% confidence intervals. There was no significant difference between DK groups in refractive sphere change from baseline (prefitting) measurements. There was no significant change across visits for either group. D = diopters.

survival curve at any given point represents the estimated probability that a subject will remain free of complications until at least that point. Under all four definitions of CLAK, the survival curves for the two Dk groups are virtually identical. The noticeable drop in the survival curves after 3 months in part may be the result of our examination schedule: subjects were generally not seen for 3 months after the dispensing of the randomized study lenses and may have experienced CLAK early on that was not detected until the first regularly scheduled quarterly follow-up visit; after that time, more opportunities may have been available to detect CLAK onset, because the clinician could note adverse symptoms at the 3-month visit and request unscheduled visits or encourage the

Table 4. Cases of Contact Lens-associated Keratopathy in the Two Lens Oxygen Permeability Groups

	Medium Oxygen Permeability Group (n = 103)					High Oxygen Permeability Group (n = 98)				
Follow-up Visit (mos)	*3*	*6*	*9*	*12*	*Total*	*3*	*6*	*9*	*12*	*Total*
Number of active subjects	79	73	66	64		79	67	64	61	
CLAK type 1 (slit-lamp findings only)	11	24	16	15	66	9	20	18	9	56
CLAK type 2 (including change in corneal curvature, refractive error)	11	45	19	7	82	12	43	14	7	76
CLAK type 3 (including subclinical findings)	12	48	18	7	85	13	47	13	5	78
CLAK type 4 (including discomfort)	15	51	16	7	89	16	48	12	5	81

CLAK = contact lens-associated keratopathy.
Shown are the number of subjects presenting with CLAK in either eye for the first time during their course of follow-up. CLAK discovered at an unscheduled visit is included in the count for the nominal follow-up visit closest to date of initial detection.

Table 5. Slit-lamp Findings by Visit

	Medium Oxygen Permeability Group (n = 103)				High Oxygen Permeability Group (n = 98)			
Follow-up Visit (mos)	*3*	*6*	*9*	*12*	*3*	*6*	*9*	*12*
No. of active subjects	79	73	66	64	79	67	64	61
Bulbar conjunctiva								
Injection	3	2	0	0	0	3	1	0
Staining	8	5	2	5	2	1	2	5
Palpebral conjunctival injection	2	0	0	0	1	1	0	1
Hypertrophy	1	2	0	1	0	0	1	1
Corneal staining								
Central	23	17	15	14	22	21	13	11
Peripheral	14	9	4	4	7	6	5	4
Corneal infiltrates	1	2	0	0	0	0	0	0
Microcysts	0	0	0	0	0	0	0	1
Striae	2	3	3	5	0	1	1	0
Polymegethism	0	0	0	1	0	0	0	0
Tear debris	1	0	0	0	1	0	0	1
Lens adherence	3	2	0	0	5	0	0	0

Shown are the number of contact lens-associated keratopathy grade cases of several possible keratopathies, stratified by visit. Subjects may have had more than one keratopathy at presentation. Actual visit dates varied from the nominal quarterly visits shown, and adverse responses observed at unscheduled or emergency visits are included in the count for the nominal visit nearest the date of initial detection.

subject to call the laboratory before the next scheduled visit to monitor developments. Table 6 shows the log-rank tests for homogeneity of survival curves. The *P* values represent the probability of observing survival curves at least as discrepant as we observed if there truly were no difference in the survival rates for the underlying populations. The relatively large *P* values confirm that there are no statistically significant differences between Dk groups in the probability of remaining free from ocular complications, regardless of the definition of CLAK used.

Also shown in Table 6 are estimates of the relative hazard of experiencing a CLAK with approximate 95% confidence limits. The relative hazard is a ratio of the group-specific hazard rates obtained from a Cox proportional hazards model. A relative hazard of 1 indicates that the risk of experiencing a CLAK is the same in the two Dk groups, whereas a relative hazard more than 1 reflects an increased risk of CLAK onset in the medium-Dk group. Table 6 shows that if we use Dk group (medium or high) as a predictor of type 1 CLAK, we obtain a relative hazard of 1.10 (0.77, 1.57),

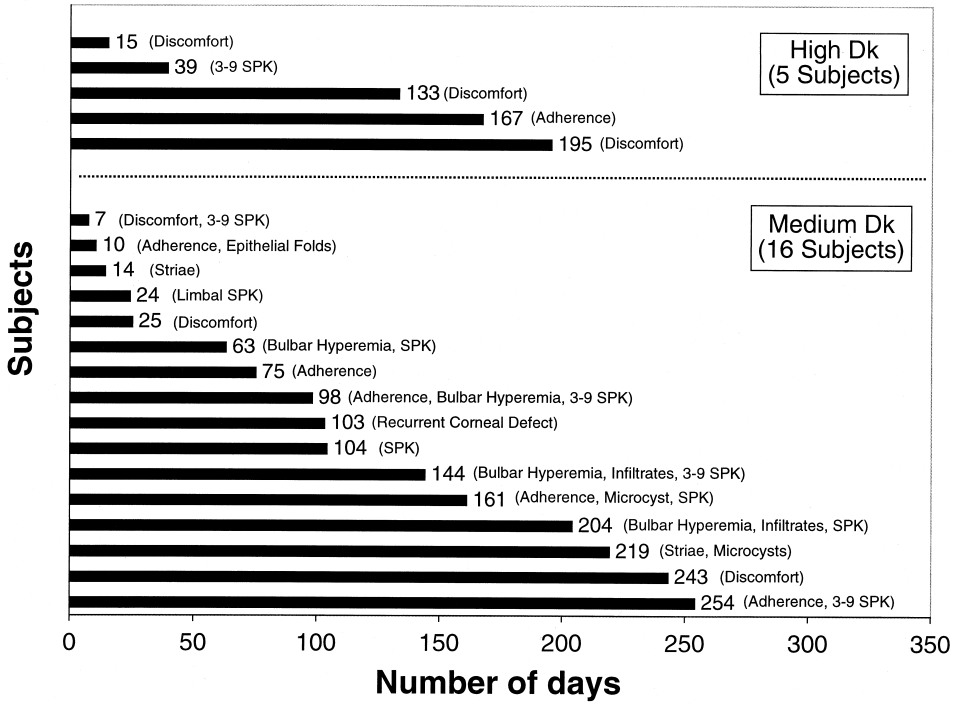

Figure 3. Sixteen subjects in the medium oxygen permeability (DK) group and 5 subjects in the high DK group failed for lens-related adverse responses. Shown for all 21 subjects are the number of days after beginning wear of the randomized study lenses that they were able to continue lens wear and the specific findings that led to termination of wear. SPK = superficial punctate keratitis.

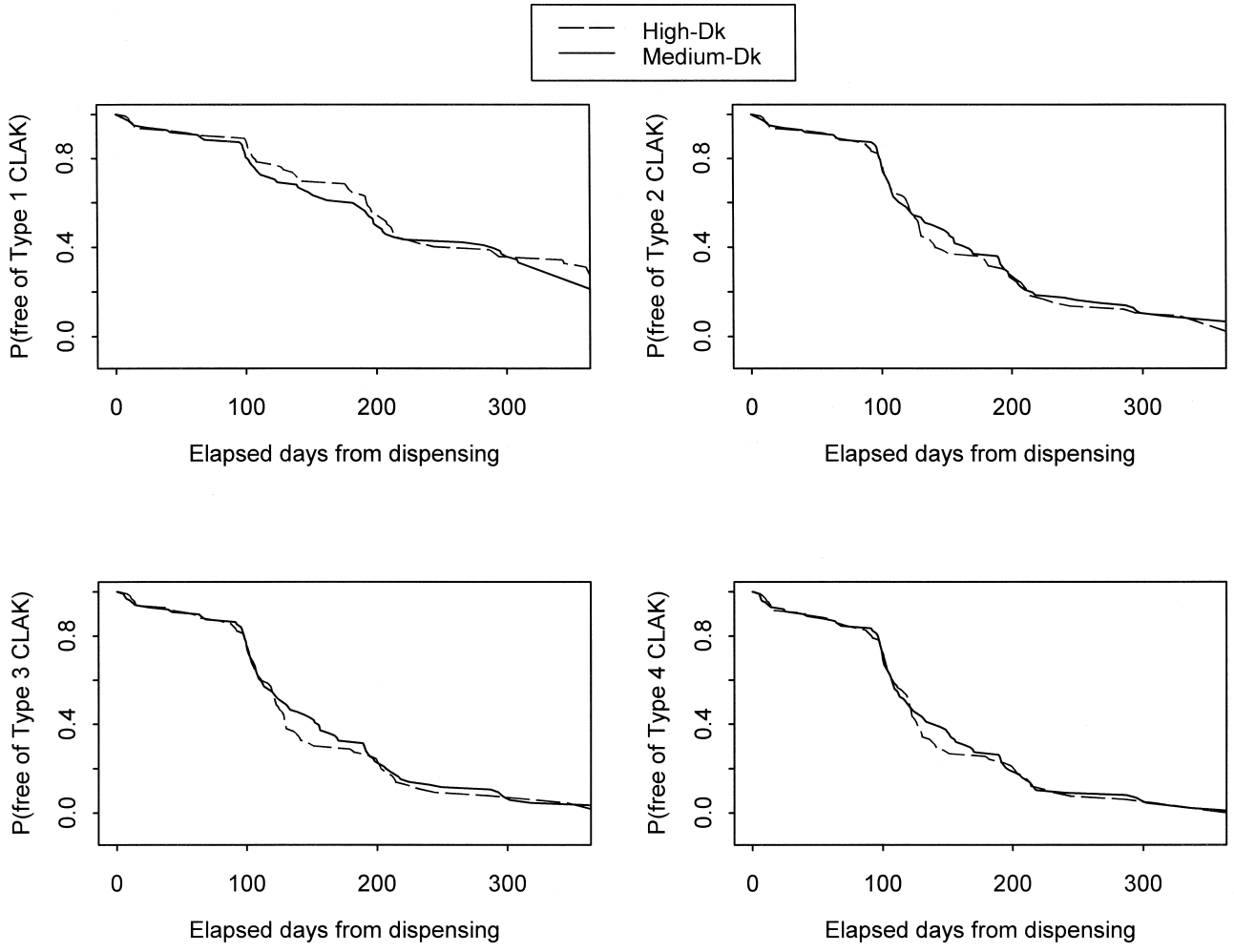

Figure 4. Survival curves showing the estimated probability of surviving free of contact lens-associated keratopathy (CLAK) are shown for four possible definitions of CLAK. Type 1 CLAK consists of slit-lamp findings and lens adherence; type 2 CLAK consists of type 1 CLAK findings or changes in refractive error or corneal curvature; type 3 CLAK consists of type 2 responses or multiple, simultaneous subclinical slit-lamp findings; type 4 CLAK consists of type 3 findings or subjective symptoms related to discomfort. Under all four definitions, there was no significant difference in probability of survival free of CLAK. DK = oxygen permeability.

indicating that subjects in the medium-Dk group do not have significantly elevated risk of experiencing type 1 CLAK compared with the high-Dk group. The upper confidence bound shows that we have sufficient statistical power to rule out (with 95% confidence) anything but a minor elevation in the risk of a type 1 CLAK associated with medium-Dk EW.

We also performed our survival analyses using the lens-specific Dk/t as a continuous predictor in addition to the Dk-group analyses. The difference in mean Dk/t between the two study groups was approximately 25 units. Using this as an example, we estimated a corresponding increased risk of 1.02 (0.76, 1.39) associated with a 25 unit decrease in Dk/t. For the other definitions of

Table 6. Survival in Rigid Gas-permeable Extended Wear Lenses to Onset of Contact Lens-associated Keratopathy

Adverse Response Type	Type 1	Type 2	Type 3	Type 4
Test of survival curves (*P* value)				
Medium vs. high oxygen permeability group	0.60	0.57	0.56	0.75
Estimated hazard ratios				
Medium vs. high oxygen permeability group	1.10	0.91	0.91	0.95
(Approximate 95% confidence interval)	(0.77, 1.57)	(0.67, 1.25)	(0.67, 1.24)	(0.70, 1.29)
Oxygen transmissibility (25 units difference)	1.02	0.89	0.90	0.94
(Approximate 95% confidence interval)	(0.76, 1.39)	(0.68, 1.16)	(0.69, 1.17)	(0.73, 1.21)

Shown are the log-rank tests of homogeneity of survival curves in the two oxygen permeability lens groups, and the estimated hazard ratios and approximate 95% confidence intervals derived from Cox proportional hazards models.

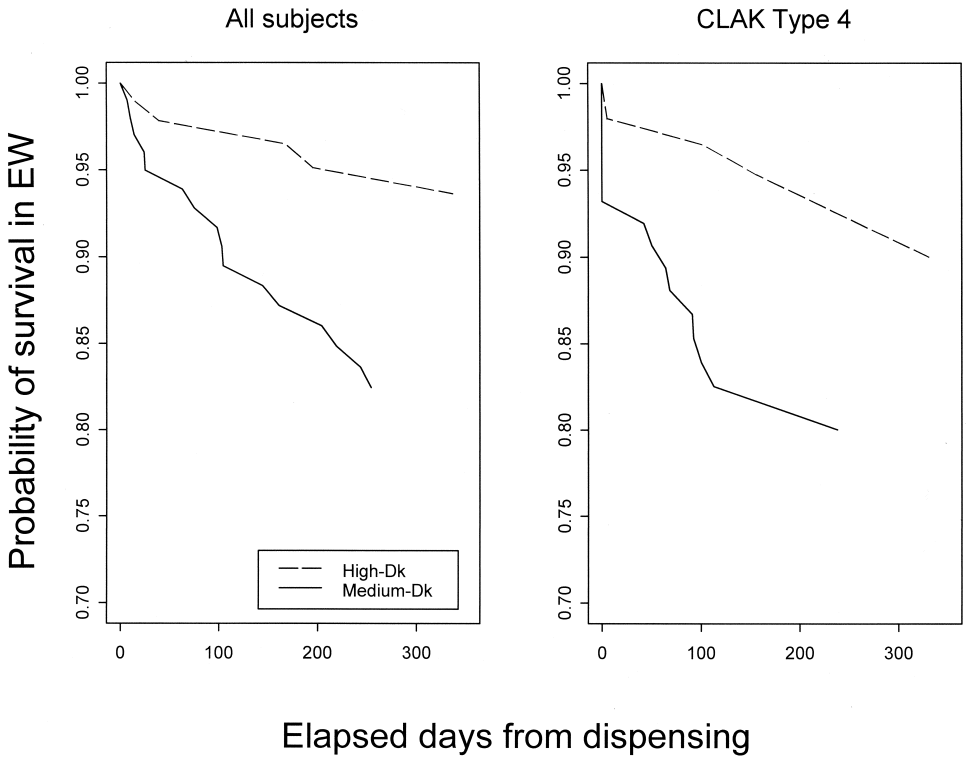

Figure 5. Survival curves showing the estimated probability of surviving in extended wear (EW) are shown for all Berkeley Contact Lens Extended Wear Study subjects and for those with contact lens-associated keratopathy (CLAK). In the first panel are survival curves for all randomized subjects, which show that the high oxygen permeability (DK) group enjoys a significantly greater probability of survival in EW; in the second panel are survival curves from time of initial onset for subjects in whom any CLAK (type 4) developed, showing that the recovery of subjects in whom CLAK develops is impeded in the medium DK group, which may explain the reduced medium DK EW survival rate despite CLAK onset rates comparable with the high DK group.

CLAK, relative hazards ranged from 0.89 (0.68, 1.16) to 0.94 (0.73, 1.21), which are consistent with the hypothesis that there is no increased risk of CLAK onset (by any of our definitions) with increased hypoxic dose.

Association of Hypoxic Dose with Failure to Maintain Rigid Gas-Permeable Extended Wear

Although the above analysis shows that hypoxic dose is not associated with development of ocular complications, this does not preclude the possibility that oxygen dose is associated with the ability to maintain 6-night RGPEW successfully, because 16 subjects completely discontinued EW due to adverse ocular response in the medium-Dk group, compared with only five in the high-Dk group.

Figure 5 (first panel) shows the survival curves for all subjects in the medium-Dk and high-Dk groups, where the time-to-outcome was defined as the time from randomization until termination from the study because of contact lens-associated adverse responses including slit-lamp findings or unresolvable lens adherence or discomfort. Subjects who exited the study before 12 months of EW because of time commitment, general disinterest, noncompliance with the study protocol, or other reasons unrelated to contact lens wear provided data censored at exit time. The survival curve for the high-Dk group dropped gradually over time, whereas the medium-Dk curve dropped more quickly, reflecting an increased risk of failure. Table 7 (first column) shows the log-rank test of homogeneity of these survival curves, which reveals that the increased probability of survival in the high-Dk group was statistically significant ($P = 0.02$). To illustrate the decreased probability of survival in the medium-Dk group, we used the survival curves to estimate the probabilities and 95% confidence bounds for survival beyond 9 months (column 1 of Table 8). The high-Dk group enjoys approximately a 13% greater probability of survival beyond 9 months compared with the medium-Dk group. From a Cox proportional hazards model (Table 7, first column), we estimated a relative hazard of 3.08 (1.13, 8.41), indicating that the

Table 7. Survival in Rigid Gas Permeable Extended Wear Lenses

	All Subjects	Subjects with any Contact Lens-associated Keratopathy (Type 4)
Test of survival curves (*P* value)		
Med. vs. high oxygen permeability group	0.02	0.01
Estimated hazard ratios		
Med. vs. high oxygen permeability group	3.08	3.26
(Approximate 95% confidence interval)	(1.13, 8.41)	(1.19, 8.92)
Oxygen transmissibility (25 units difference)	2.62	2.70
(Approximate 95% confidence interval)	(1.10, 6.23)	(1.14, 6.42)

Shown are the log-rank tests of homogeneity of survival curves in the two oxygen permeability lens groups and the estimated hazard ratios and approximate 95% confidence intervals derived from Cox proportional hazards models.

Table 8. Estimated Probabilities (%) of Survival in Extended Wear beyond 9 Months for All Subjects, and Survival for More Than 9 Months after Initial Onset for Those Who Experienced a Contact Lens-associated Keratopathy Event (Type 4)

	All Subjects	Subjects with Any Contact Lens-associated Keratopathy (Type 4)
Medium oxygen permeability	82.5 (74.7, 90.3)	77.7 (67.4, 87.9)
High oxygen permeability	95.2 (90.6, 99.8)	94.1 (88.4, 99.7)

Approximate 95% confidence bounds are included in parentheses.

medium-Dk group experienced more than three times the risk of EW failure than the high-Dk group. Using the mean subject-specific Dk/t (i.e., taking individual lens thickness into account) as a continuous predictor of RGPEW failure, we obtained a relative hazard of 2.62 (1.10, 6.23) for a 25-unit decrease in Dk/t. From these results, we concluded that hypoxic dose does significantly affect the probability of successfully maintaining 6-night RGPEW.

It is possible that the decreased probability of successful EW in the medium-Dk group, despite comparable rates of initial onset of CLAK in the two groups, is because of the fact that CLAK is more likely to result in complete discontinuation of EW for the medium-Dk subjects. To test this hypothesis, we examined the duration of successful EW from the time of initial onset of any CLAK (type 4) to determine whether the probability of continued survival in EW after experiencing a CLAK was greater in the high-Dk group.

Figure 5 (second panel) depicts the probability of further survival in EW after experiencing a type 4 CLAK, which is significantly greater in the high-Dk group ($P = 0.01$). Table 8 (second column) illustrates this difference by showing that the probability of survival for more than 9 months after experiencing a CLAK is approximately 16% greater in the high-Dk group. The relative hazard estimate (Table 8, second column) shows that the medium-Dk group experienced more than three times the risk of failing in EW after first experiencing a CLAK. These results support the hypothesis that the decreased survival probability among medium-Dk wearers, when risk of CLAK onset appears to be comparable, may be the result of a hypoxic effect on recovery from CLAK after it develops.

Conclusions

Our primary objectives were to determine whether substantially reducing corneal hypoxia during RGPEW lowers the incidence of CLAK, failure to maintain EW for 12 months, or both. Our results suggest that increasing the level of oxygen available to the cornea during RGPEW significantly increases the chances of maintaining successful extended contact lens wear for 12 months. Our best estimate of the increased risk of failure with the lower oxygen lenses is approximately threefold; the upper confidence bound suggests that this could be as large as eightfold. However, our results also suggest that the probability of CLAK developing is not significantly greater with the lower oxygen lenses. These results at first seem paradoxical: why would there be a dramatic elevation in the risk of failure in the medium-DK group if both groups demonstrate comparable initial CLAK rates?

One possible explanation is that subjects in the medium-Dk group in whom CLAK did develop were less likely to recover. The analysis of EW survival rate among those subjects who experienced CLAK supports this hypothesis, showing that recovery from CLAK and continued successful RGPEW is less likely under the greater hypoxic dose. It is possible that the greater dose of hypoxia induced by the medium-Dk lenses limited the successful resumption of EW after recovery from an adverse response. Consistent with this possibility is the observation that five subjects who were randomized to the medium-Dk lenses (after successfully adapting to EW with the high-Dk adaptation lenses) began to experience recurring, persistent lens adherence that eventually required discontinuation of EW, whereas only one of the five high-Dk subjects who experienced adherence was unable to continue EW after intervention. Is it possible that hypoxia may in some way be linked to lens adherence? This speculation requires further investigation.

It is also possible that although the two Dk groups exhibited similar overall numbers of initial CLAK events, these events were more severe, on average, in the medium-Dk group, or tended to recur more often after resumption of EW. We determined from a post hoc examination of the CLEWS data that the severity of responses categorized as CLAK did not differ between groups; however, we cannot establish whether CLAK recurred more often under the lower oxygen condition from the CLEWS data, for several reasons discussed in detail above.

A third possible explanation for these results is that our definitions of CLAK did not distinguish between types of keratopathy that could be more or less resistant to treatment and eventually require complete discontinuation of EW. Although far from conclusive, the observation of infiltrates and striae in the medium-Dk group, which were mostly absent in the high-Dk group, are consistent with this possibility.

In summary, we suggest that the most likely explanation for the differences in survival rates between our two study groups is that the medium-Dk group experienced more of the types of keratopathies that are most difficult to reverse (e.g., lens adherence, persistent corneal staining, infiltrates) and that, after intervention, successful return to EW was less likely for the medium-Dk group because of the continued hypoxic exposure. Whatever the exact explanation for the differences in overall EW success, the clinical implication is clear: Although Food and Drug Administration-approved RGPEW lenses are available in a wide range of Dk ($40-92 \times 10^{-11}$ (cm^2/second)(ml 0_2/ml $\times$ mmHg)), the clinician should prescribe the highest oxygen permeable lens available to increase the probability for success. As a caution, we note that these data include only a 1-year period of observation of subjects recruited from the University of California Berkeley campus and surrounding community and enrolled based on CLEWS eligibility criteria. Thus, generalizing these findings to longer periods of wearing time or to materially different populations requires further study.

The clinical outcomes we have observed in CLEWS provide some interesting and possibly important information about complications accompanying SCLEW. Our findings are in agreement with other clinical studies on RGPEW, which show lower incidence and severity of contact lens-associated complications compared with SCLEW, even though the oxygen transmissibility of the medium-Dk lenses in CLEWS is comparable with that of disposable SCLEW lenses.[8–10] A comparison of CLEWS outcomes with historical results from SCLEW indicates that, compared with RGPEW, SCLEW appears to place the patient at considerably higher risk for serious and vision-threatening ocular morbidity. For example, a recent study on disposable SCLEW reported that over a 13-month follow-up period, among 100 patients there were 44 cases of infiltrative keratitis that were associated with acute red eye, peripheral corneal ulcers, keratoconjunctivitis, and other types of ocular morbidity.[7] In contrast, of the 201 subjects in CLEWS, there were only 3 cases of infiltrates and no acute red eyes or infections.

How can we explain these large differences in complications between RGPEW and SCLEW when the cornea is exposed to approximately the same oxygen levels? Perhaps the answer is related to differences in lens performance and not hypoxia alone. For example, when the eyes are closed, there is no tear exchange and debris builds up between the cornea and lens for both rigid and soft lenses. However, as soon as the eyes are open, the trapped debris under the rigid lens is removed within a few blinks because of the good tear exchange; unfortunately, this is not the case for soft lenses, which have very poor tear mixing.[11] We propose that in SCLEW, epithelial integrity may be affected because of the persistence of trapped debris. This hypothesis is consistent with recent studies showing that closed-eye soft lens wear can result in a substantial increase in the permeability of the epithelium to fluorescein.[12,13]

In summary, although overnight contact lens wear should be recommended with caution and carefully monitored for early detection of ocular complications, it appears that high-Dk RGP lenses can be a relatively safe and effective treatment for RE. The overall RGP success rate among subjects who already adapted to overnight wear (approximately 62%) was reasonably good considering the burdens of study participation and the lack of any monetary investment on the part of the patients, and most of those not completing 1 year of EW exited the study for reasons unrelated to lens wear (e.g., unwillingness to continue the time commitment required by the study). However, we note a substantial drop-out rate from the beginning of the fitting process to successful EW adaptation (545 subjects fit, 201 successfully adapted to EW). Failure to adapt to EW for reasons unrelated to the study protocol seems more often to be the result of discomfort (approximately 34%) than of serious corneal responses to overnight lens wear (approximately 17%). This suggests that if improved fitting strategies of rigid materials could be developed to provide improved comfort, RGPEW of high-Dk materials may be a viable treatment for patients who desire EW.

Acknowledgments: The authors thank the contributions of the members of the Data and Safety Monitoring Board (Joan Hilton, ScD, DSMB, Committee Chair, Department of Epidemiology and Biostatistics, University of California San Francisco; David Heiden, MD, School of Optometry, University of California Berkeley; Arthur L. Reingold, MD, School of Public Health, University of California Berkeley; Barry Weissman, OD, PhD, Department of Ophthalmology, University of California Los Angeles School of Medicine; and Barbara Woodruff, Chief Administrative Officer, School of Optometry, University of California Berkeley). We also thank John Fiorillo, who provided technical assistance in the preparation of this article.

References

1. Miller RG Jr. Survival Analysis. New York: Wiley, 1981; 143–6.
2. SAS/STAT User's Guide, Version 6, 4th ed. Vol. 2. Cary, NC: SAS Institute, Inc. 1989.
3. Young G, Port M. Rigid gas-permeable extended wear: a comparative clinical study. Optom Vis Sci 1992;69:214–26.
4. MacKeen DL, Sachdev M, Ballou V, Cavanagh HD. A prospective multicenter clinical trial to assess safety and efficacy of Menicon SF-P RGP lenses for extended wear. CLAO J 1992;18:183–6.
5. Chalupa E, Swarbrick HA, Holden BA, Sjöstrand J. Severe corneal infections associated with contact lens wear. Ophthalmology 1987;94:17–22.
6. Mondino BJ, Weissman BA, Farb MD, Pettit TH. Corneal ulcers associated with daily wear and extended wear contact lenses. Am J Ophthalmol 1986;102:58–65.
7. Sankaridurg PR, Sweeney DF, Sharma S, et al. Adverse events with extended wear of disposable hydrogels: results for the first 13 months of lens wear. Ophthalmology 1999;106:1671–80.
8. Stapleton F, Dart JKG, Minassian D. Risk factors with contact lens related suppurative keratitis. CLAO J 1993;19:204–10.
9. Maehara JR, Kastl PR. Rigid gas permeable extended wear [review]. CLAO J 1994;20:139–43.
10. Fonn D, Holden BA. Rigid gas-permeable vs. hydrogel contact lenses for extended wear. Am J Optom Physiol Opt 1988;65:536–44.
11. McNamara NA, Polse KA, Brand RJ, et al. Tear mixing under a soft contact lens: effects of lens diameter. Am J Ophthalmol 1999;127:659–65.
12. McNamara NA, Fusaro RE, Brand RJ, Polse KA. Epithelial permeability reflects subclinical effects of contact lens wear. Br J Ophthalmol 1998;82:376–81.
13. McNamara NA, Polse KA, Fukunaga SA, et al. Soft lens extended wear affects epithelial barrier function. Ophthalmology 1998;105:2330–5.